CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761195Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 132953

MEETING MINUTES

Argenx BV
Attention: Lavonne Patton, PhD
Director, Cardinal Health Regulatory Sciences
US Agent
7400 W 110th Street, Suite 300
Overland Park, KS 66210

Dear Dr. Patton:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ARGX-113.

We also refer to the telecon between representatives of your firm and the FDA on August 5, 2020. The purpose of the meeting was to discuss a planned BLA submission.

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact Michael Matthews, Regulatory Project Manager, at Michael.Matthews@fda.hhs.gov or at (301) 796-3047.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Director (Acting)
Division of Neurology 1
Office of Neuroscience
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-BLA

Meeting Date and Time: August 5, 2020, 12:00 PM to 1:00 PM
Meeting Location: Teleconference

Application Number: 132953
Product Name: ARGX-113
Indication: For the treatment of myasthenia gravis
Sponsor Name: Argenx BV
Regulatory Pathway: 351(a)

FDA ATTENDEES

Division of Neurology 1
Eric Bastings, MD, Director (Acting)
Teresa Buracchio, MD, Deputy Director (Acting)

Office of Clinical Pharmacology, Division of Clinical Pharmacology I
Sreedharan Sabarinath, PhD, Clinical Pharmacology Team Leader
Bilal AbuAsal, PhD, Clinical Pharmacology Reviewer

Division of Pharmacology/Toxicology - Neuroscience
Lois Freed, PhD, Acting Director

Office of Biostatistics
Kun Jin, PhD, Statistical Team Leader, Biometrics I

Division of Regulatory Operations for Neuroscience
Michael Matthews, Regulatory Project Manager
Susan Daugherty, Senior Regulatory Health Project Manager

Office of Surveillance and Epidemiology (OSE)
Briana Rider, PharmD, CPPS, Team Leader, Division of Medication Error Prevention and Analysis (DMEPA)
Chad Morris, PharmD, MPH, Safety Evaluator, DMEPA
Casmir Ogbonna, PharmD, MBA, BCPS, BCGP, Safety Regulatory Project Manager
Ingrid Chapman, PharmD, Risk Management Analyst, Division of Risk Management (DRM)

SPONSOR ATTENDEES

Wim Parys, MD, Chief Medical Officer
Antonio Guglietta, MD, Vice President Clinical Development
Jon Beauchamp, MD, Vice President Medical Affairs
Judith Baumeister, PhD, Head of Toxicology and Nonclinical Pharmacology
Peter Ulrichts, PhD, Scientific Lead Neuromuscular Franchise
(b) (4) Clinical Pharmacologist (consultant)
Tony Vangeneugden, PhD, Head of Biostatistics
Caroline T'joen, MSc, Senior Biostatistician
(b) (4) Program Manager (consultant)
Stefan Ochalski, PhD, Vice President Regulatory Affairs
Adeline Boucher, PharmD, Director Regulatory Affairs
Monika Van Den Haute, MSc, Senior Regulatory Affairs Manager

1.0 BACKGROUND

Argenx has developed ARGX-113 (INN: efgartigimod alfa) for the treatment of adult patients with generalized myasthenia gravis. On May 22, 2020, Argenx submitted a request for a pre-BLA meeting to discuss the clinical and nonclinical sections of a planned biologics license application (BLA). FDA granted the meeting on June 9, 2020. The meeting package includes the proposed scheduled for a rolling BLA submission, with clinical and nonclinical information proposed to be submitted in September 2020, and the quality information proposed to be submitted in October 2020.

Orphan drug designation status for this indication was received on September 20, 2017, and fast track designation was granted on February 18, 2020.

FDA sent Preliminary Comments to Argenx on July 24, 2020.

2.0 DISCUSSION

2.1. Clinical

Question 1: Does the Agency agree that a statistically significant difference ($p<0.0001$) in the phase 3 pivotal study ARGX-113-1704 in terms of the primary endpoint (%total MG-ADL responders) has been demonstrated and that this single study can form the basis for approval of efgartigimod treatment in the proposed indication, ie, adult patients with generalized myasthenia gravis?

FDA Response to Question 1:

A single trial can be the basis for marketing approval under specific circumstances discussed in the Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.[1]

On face, the efficacy results from study ARGX-113-1704 may be adequate to support the submission of marketing application, but the acceptability of a single trial to support drug approval would be a review issue after BLA submission. However, you would also need to address the safety requirements for a BLA submission discussed in the response to Question 4.

Additionally, a future marketing application should include an efficacy analysis in the subset of AChR-antibody seronegative patients.

Discussion:

There was no further discussion at the meeting.

Question 2: Does the Agency agree to change the test statistics that was planned per protocol to compare efgartigimod and placebo with respect to time to qualification for retreatment?

FDA Response to Question 2:

We do not agree to change the test statistics post hoc based on observed data. The planned log-rank test is a valid test without proportional hazards assumption.

Discussion:

There was no further discussion at the meeting.

Question 3: Does the Agency agree with the sponsor's proposed approach for the presentation of efficacy data in the Summary of Clinical Efficacy (SCE)? The Integrated Summary of Efficacy (ISE) is planned to be included in the SCE.

FDA Response to Question 3:

It is unclear to us if the pooled efficacy analysis will provide useful information given the varied designs of the studies. You may include a pooled analysis of efficacy in the submission in addition to the individual study results; however, our efficacy review would focus on the data from the Phase 3 study.

[1] https://www.fda.gov/media/71655/download

Discussion:

There was no further discussion at the meeting.

Question 4: Does the Agency agree with the proposed safety database included at the time of the planned BLA?

FDA Response to Question 4:

We do not agree. Your proposed safety database will not be adequate to support the submission of a BLA. In Table 5 of the briefing document, you report only 15 subjects with at least 12 months of follow-up for safety. Considering the prevalance of myasthenia gravis, your submission should be consistent with ICH E1 requirements that specify that 100 subjects be exposed to the drug for a minimum of one-year as part of a safety database.

Additionally, as discussed at the End of Phase 2 meeting on April 17, 2018, it is required that "at least half of the safety consist of patients dosed with the highest anticipated dose and frequency of dosing." Based on your response to the information request submitted on July 21, 2020, more than half (50/96) of the patients exposed to efgartigimod have required 4 or more cycles of treatment during at least 6 months of follow-up (i.e., a treatment cycle of approximately every 6 weeks). Therefore, we anticipate that you will need, at a minimum, 12 months of safety data from approximately 50 subjects treated with a frequency of at least one cycle every 6 weeks (i.e., 8 cycles in 12 months), in addition to 12 months of safety data from 50 subjects at any treatment cycle frequency. A separate safety study or a modification to the ongoing open-label study to include regularly scheduled dosing (e.g., every 6 weeks) could provide the necessary safety data.

Discussion:

The sponsor presented additional information that a data-cutoff in October 2020 would be able to provide data from 80 to 89 patients with a follow-up of at least 12 months. The sponsor proposed that this data could be submitted to the NDA as a safety update report.

The sponsor also presented data that the median dosing frequency in the current dataset was approximately every 7 weeks, and that it was anticipated that the highest dosing frequency would be approximately 7 cycles per year. As of the proposed data cut-off in October 2020, the sponsor anticipates that they will have approximately 45 to 50 patients (of the 80 to 89 patients total) who will have received 7 cycles of treatment with a follow-up of at least 12 months at the time of the safety update.

The Division agreed to the proposed size of the database and dosing frequency (i.e., 80 to 89 patients with a follow-up of at least 12 months, with 45 to 50 of those patients having received at least 7 cycles of treatment); however, in order to allow adequate time for review, the data will need to be provided at the time of the NDA submission and it will not be acceptable to submit it as a safety update.

Question 5: Does the Agency agree with the proposed content for the safety update and the timing of safety update submission?

FDA Response to Question 5:

You propose submitting the safety update as a 90-day safety update rather than a 120-day safety update, and to include TEAEs, clinical laboratory data, vital signs, ECGs, immunogenicity data, safety narratives, and pooled safety data from the Phase 2 and 3 studies. This plan may be acceptable, and can be considered once you have adequate safety data, as discussed in the response to Question 4.

Discussion:

See discussion under Question 4.

Question 6: Does Agency agree with the sponsor's proposal regarding safety narratives and individual case report forms and with the proposed approach to the presentation of adverse events of special interest (AESI) in the planned BLA?

FDA Response to Question 6:

Your plan to provide safety narratives, CRFs, and AESIs is reasonable. Also, see response to Question 4.

Also, please refer to the standard pre-BLA safety requests in Attachment 1. We note that not all requests may be applicable to your program; however, you should attempt to address the requests that are applicable.

Discussion:

There was no further discussion at the meeting.

Question 7: Does the Agency agree that a risk Evaluation and Mitigation Strategy (REMS) or Medication Guide will not be required for efgartigimod, if approved for the proposed indication, and that the risks associated with treatment with efgartigimod can

be managed adequately with appropriate labeling and routine pharmacovigilance activities?

FDA Response to Question 7:

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

Discussion:

There was no further discussion at the meeting.

Question 8: Does the Agency agree with the sponsor's proposed approach for the presentation of safety data in the Summary of Clinical Safety (SCS)? The Integrated Summary of Safety (ISS) is planned to be included in the SCS.

FDA Response to Question 8:

With respect to the safety pools, we note that the proposed pools may each contribute to the understanding of safety. Please base your primary analysis on the pivotal phase 3 study with the safety pools included as supportive information. Also, see response to Question 4.

Discussion:

There was no further discussion at the meeting.

Question 9: Does the Agency agree with the proposed Study Data Standardization Plan (SDSP) for the nonclinical and clinical studies?

FDA Response to Question 9:

From a technical standpoint, the proposed Study Data Standardization Plan (SDSP) for the nonclinical and clinical studies is acceptable.

Discussion:

There was no further discussion at the meeting.

2.2. Regulatory

Question 10: Does the Agency agree with the content and presentation of the BLA in support of efgartigimod for the treatment of patients with generalized myasthenia gravis (gMG)?

FDA Response to Question 10:

In general, the planned content and presentation of the BLA appear adequate, once you have adequate safety data, as discussed in the response to Question 4.

Your justification for not conducting studies to assess the carcinogenic potential of efgartigimod is still under review. A response will be provided by July 31, 2020.

Discussion:

There was no further discussion at the meeting.

Question 11: Does the Agency agree with the sponsor's proposal and schedule for submission of the CTD modules on a rolling basis?

FDA Response to Question 11:

Although rolling submission is allowed as part of Fast Track designation, it is premature to discuss specific submission dates, given the concerns with the safety database discussed in the response to Question 4.

Discussion:

The sponsor asked for the timeframe for review of a rolling review request. The Division indicated that it this is typically 60 days but would confirm in a post-meeting comment. Typically, the Agency is able to review these requests more quickly than the 60-day period. The Division noted that each component of the rolling submission should contain complete eCTD modules.

Post-meeting Comment: FDA targets 60-days for a rolling review determination per the MAPP. For more information on the process for rolling review, refer to Appendix 2 of the guidance for industry Expedited Programs for Serious Conditions – Drugs and Biologics.
https://www.fda.gov/files/drugs/published/Expedited-Programs-for-Serious-Conditions-Drugs-and-Biologics.pdf

Question 12: Does the Agency agree with the proposal for submission of BIMO listings?

FDA Response to Question 12:

You have proposed to include clinical study level information and subject-level data line listings by clinical site for studies ARGX-113-1704 and ARGX-113-1705, but not the summary-level clinical site dataset (clinsite). While submission of the clinsite dataset is currently optional, this dataset is useful in the Agency's decision-making for clinical site inspections.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf

Discussion:

There was no further discussion at the meeting.

Question 13: The sponsor plans to request Priority Review for the planned BLA for efgartigimod in myasthenia gravis. Does the Agency agree that this BLA submission is eligible for Priority Review?

FDA Response to Question 13:

A request for priority review of your application will be considered at the time of filing, taking into account the information available at that time. We also remind you that there is available therapy for gMG; therefore, a request for priority review should describe how your product addresses an unmet need compared to available therapy.

Discussion:

There was no further discussion at the meeting.

Question 14: The sponsor believes an Advisory Committee will not be required for efgartigimod in support of the myasthenia gravis indication. Does the Agency agree?

FDA Response to Question 14:

A determination regarding the need for an Advisory Committee meeting will be determined during review of your complete marketing application.

Discussion:

At this time, the Division has not made any decision regarding the need for an Advisory Committee and that will be determined during the BLA review.

Question 15: Is the Agency planning to schedule an application orientation meeting with the sponsor?

FDA Response to Question 15:

It is not common for the Division of Neurology 1 to request an application orientation meeting. The need for that meeting will be considered after your application has been submitted.

Discussion:

There was no further discussion at the meeting.

Additional Clinical Pharmacology Comment:

For submitting the population PK modeling report, please follow the expectations listed here:

https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/modeldata-format

Nonproprietary Name Suffix

Sponsor Question:

Argenx submitted a request for review of the four-letter suffix on July 10, 2020. Can the Agency clarify when Argenx might receive confirmation whether the proposed suffix was accepted?

FDA Response:

FDA reviews any submitted proposed suffixes as resources permit if submitted during the IND phase. We are in the process of reviewing your proposed suffixes. Once we complete the evaluation of your suffixes, we will notify you of our decision in a letter.

BLA License Number

The sponsor asked for the timeframe in which they would receive a license number. The Division stated they would provide the answer after the meeting.

Post-meeting comment:

The US license number would be provided as part of the approval letter.

Additional Clinical Post-meeting comment:

Appendix 1 contains general clinical safety analyses that are requested for NDA and BLA submissions to DN1. Your BLA submission should address the analyses that are applicable to your program.

3.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

We did not have a preliminary discussion on the need for a REMS, other risk management actions or the development of a Formal Communication Plan
Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

BLA NUMBER: LATE COMPONENT - QUALITY

In addition, we note that a Quality pre-submission meeting occurred on July 22, 2020. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[2] and Pregnancy and Lactation Labeling Final Rule[3] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

- Regulations and related guidance documents.

[2] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[3] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- A sample tool illustrating the format for Highlights and Contents, and

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing

of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[4]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[5]

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such

[4] http://www.fda.gov/ectd
[5] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the guidance for industry *Assessment of Abuse Potential of Drugs*.[6]

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

[6] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[7] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[8]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[9]

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA.

[7] https://www.fda.gov/media/84223/download
[8] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and
[9] https://www.fda.gov/media/85061/download

FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

To the extent that your proposed 351(a) BLA is within the scope of this guidance, FDA will assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues requiring further discussion.

5.0 ACTION ITEMS

The action items identified during the meeting have been completed and are included in these meeting minutes.

6.0 ATTACHMENTS AND HANDOUTS

The following attachments are provided below:

1. FDA's response to question 6 with the standard pre-BLA safety requests.
2. Argenx responses and clarifications to FDA pre-BLA minutes
3. Argenx slides related to question 4

Attachment 1.

DN1 Pre-BLA and Pre-NDA Meetings
General Clinical Safety Requests

Datasets:

1. Each individual subject should be assigned a single unique subject identifier across the entire application (e.g., including open label extensions of the trials). Include the unique subject identifier in the ISS and individual studies' datasets.
2. Submit datasets for all Phase 1, Phase 2, Phase 3 studies (including open label extension studies), including the Phase 2 and 3 studies performed for indications other than the one proposed for this application.

For additional guidance refer to the FDA webpage on Study Data Standards Resources.

General Submission Contents:

1. Follow the requirements noted in 21CFR 314.50 (d)(5)(vi), Summary of Safety Information and the Guideline for the Format and Content of the Clinical and Statistical Sections of an Application
2. Provide an assessment of safety as per the FDA Guidance for Industry: Premarketing Risk Assessment
3. Include a copy of each clinical study protocol as well as each amended protocol. Provide a list of the inclusion and exclusion criteria for each of the studies, including those introduced as part of protocol amendments. Please submit all versions of the protocols (and Statistical Analysis Plan) and the date when changes were implemented. Please ensure that a Summary of Changes for each version is included.
4. In addition to the comprehensive analyses performed for the pivotal trials, the ISS should also comprehensively integrate safety analyses for all other study group pools for treatment-emergent adverse events (TEAEs), deaths, serious adverse events, discontinuations for TEAEs, TEAEs of special interest, subgroups, and vital sign/laboratory/ECG measurements.
5. Submit a table detailing all of the tables and figures featured in the clinical efficacy and safety sections of the application. The table should contain the following:
   a. Title of the table or figure in the application
   b. A hyperlink to the location of the table or figure with page number
   c. A hyperlink to the SAS code used to create the table or figure (including information regarding the datasets that were used)
6. Format the tables of the ISS according to examples in FDA's Reviewer Guidance – Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review.
7. Include active hyperlinks from the lists of references to the referenced article.

8. Provide DSMB meeting minutes (including any data/slides presented). For those meetings that were cancelled or meetings where no minutes were taken, please include a place holder for that meeting noting such and signed by a member of the clinical team. Please also ensure that these packages come with a table of contents and are bookmarked by date.
9. Include information regarding important regulatory actions in other countries and foreign labeling (translated, if applicable).
10. Submit an annotated version of the pre-BLA meeting minutes that include hyperlinks, when applicable, to the analysis and/or documents requested.

Adverse events:

1. Follow the coding rules for MedDRA in the ICH-endorsed "MedDRA Term Selection: Points to Consider" document accessible at MedDRA
2. For each of the studies, the submitted datasets should contain both the verbatim terms and the MedDRA coding with all levels of the MedDRA hierarchy. For each adverse event, MedDRA coding should be provided for the primary MedDRA path.
3. Provide a summary table of the original AE coding dictionaries that were used in each of the trials.
4. The preparation of the adverse event dataset for the ISS should include MedDRA Preferred Terms from a single version of MedDRA.
5. Ensure that all adverse events are presented, and not only events deemed "drug-related."
6. Provide a table of treatment-emergent adverse events reported in ≥ 2% of subjects (after rounding) in any drug treated dose group (and greater than placebo) sorted by MedDRA SOC (in alphabetical order) and then by MedDRA Preferred Term.
7. Provide a table which summarizes the outcomes of all pregnancies. Provide a table which summarizes all known adverse events in subject offspring.

Narratives and Case Report Forms (CRFs):

1. Provide narratives and case report forms for deaths, adverse events leading to drug discontinuation, SAEs, pregnancies, and AEs of special interest. You should be prepared to supply any additional CRFs or narratives with a rapid turnaround upon request. Narratives should be integrated. For subjects who had more than one event requiring a narrative (whether in the same trial or in the core study and an extension) present a single narrative (rather than separate narratives for the various events).
2. Include a word file (and excel spreadsheet) that indicates those subjects for whom you submitted a case report form and/or narrative. This file should include an indicator for whether each item was submitted and the reason why it was submitted along with hyperlinks to the narrative and CRF.
3. Provide reports for any autopsies conducted during any of the studies.

4. Provide a line listing, narrative, and case report form for all subjects who fit the Hy's Law laboratory criteria.
5. Note that CRFs should include all clinical documents collected about the patient regardless of whether you label them "CRFs", e.g., Medwatch/CIOMS forms, event fax coversheets, SAE or event worksheets, narrative worksheets, data queries, etc.
6. Provide a tabular listing of all subjects with all discontinuations, sorted by reason. The table should include columns for study number, treatment group, unique subject ID, primary reason for drug or study discontinuation. For reasons including Lost to follow-up, Other, Physician/investigator decision, Withdrew consent, and Patient decision, provide more specific information regarding the discontinuation. The Division may want to request selected narratives/CRFs from some of these patients, but they do not need to be submitted at the time of the initial NDA/BLA submission.
7. Narrative summaries should provide a complete synthesis of all available clinical data and an informed discussion of the case. The narratives should be comprehensive enough for the reader to come to a reasonable conclusion regarding the subject and the adverse event. The following items should be included (but not limited to):
    a) Patient age and gender
    b) Adverse event onset and stop dates (presented as relative Study Day number)
    c) Signs and symptoms related to the adverse event being discussed
    d) An assessment of the relationship of exposure duration to the development of the adverse event
    e) Pertinent medical history
    f) Concomitant medications with start dates relative to the adverse event
    g) Pertinent physical exam findings
    h) Any abnormal vital sign measurements
    i) Pertinent test results (e.g., lab data, ECG data, procedures, biopsy data, autopsy results)
    j) Discussion of the diagnosis as supported by available clinical data
    k) For events without a definitive diagnosis, a list of the differential diagnoses
    l) Treatment provided
    m) Re-challenge results (if performed)
    n) Outcomes and follow-up information

Laboratory and Vital Sign Measurements:

1. Refer to the following FDA webpage for the CDER position on use of SI units for lab tests:
   SI Units.
2. Provide the normal reference ranges for every laboratory value.
3. Clearly list the normal values, as well as the thresholds for analysis of outliers, for outlier analyses of laboratory data, vital signs, and ECG data.

4. When possible, use the latest version of the National Institutes of Health (NIH) Common Terminology Criteria for Adverse Events (CTCAE) for toxicity grades and shift analyses.
5. Report the number and percentage of subjects with at least one post-treatment vital sign measurement meeting any of these criteria:
   - Systolic Blood Pressure: <90 mmHg, >140 mmHg, >160 mmHg
   - Diastolic Blood Pressure: <50 mmHg, >90 mmHg, >100 mmHg
   - Pulse Rate: <60 bpm, >100 bpm
   - Body Weight: decrease of ≥7% from baseline and increase of ≥7% from baseline
   - Temperature: >38.0 °C, <36.0 °C
   - Respiratory rate: <12 breaths/min, > 20 breaths/min
6. Summarize the protocols for collecting ECG data. Summarize the frequency of post-treatment QTc >450 ms, >480 ms, and >500 ms.

Other requests:

1. Patient profiles
   Submit individual patient profiles containing all laboratory and other study results in a single place for each patient. Provide this information for patients who died, had a serious adverse event, discontinued from the trial due to an adverse event, or had a medically significant event for which a narrative is submitted. Include all the information recorded for that patient, including but not limited to:
   a) Age
   b) Sex
   c) Dates of screening, randomization and starting therapy
   d) Whether the patient completed or did not complete the study, with dates and reason for withdrawal
   e) Adverse events (reported term, preferred term, start and stop date [with relative study day], seriousness, outcome, whether it resolved or not and action taken with drug)
   f) Prior medications and concomitant medications with dates of start and end
   g) Vital signs and laboratories, sorted by date, with reference ranges *
   h) Autopsy reports for all deaths. (If an autopsy report is not available, explicitly state this.)
   i) Full reports for radiologic studies, ECG, MRI, pathology results, special studies and procedures with dates and reference ranges
   j) Provide relevant results obtained outside of clinical trial visits, including those obtained during hospitalization or emergency room visits, in each patient file. Also include baseline study results.
   k) For patients who had IND safety report(s), include dates when the initial and follow up safety reports were submitted.

Create a PDF file for each patient and a table of contents with links to each assessment for each patient.

2. Please submit for Division comments an example narrative from a patient who had more than one serious adverse event and participated in the controlled and extension studies prior to submitting your NDA.
3. We request that you submit a sample integrated summary of safety datasets (with data definition file) for Division comments prior to submitting the NDA. This process could help to identify and resolve any potential issues of navigability or interpretability that could impact the review of your application.

Attachment 2.

Argenx responses and clarifications to FDA pre-BLA minutes

	Sponsor Original Question	FDA Response	Argenx position/clarification
1	Does the Agency agree that a statistically significant difference (p<0.0001) in the phase 3 pivotal study ARGX-113-1704 in terms of the primary endpoint (%total MG-ADL responders) has been demonstrated and that this single study can form the basis for approval of efgartigimod treatment in the proposed indication, ie, adult patients with generalized myasthenia gravis?	A single trial can be the basis for marketing approval under specific circumstances discussed in the Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.[1] On face, the efficacy results from study ARGX-113-1704 may be adequate to support the submission of marketing application, but the acceptability of a single trial to support drug approval would be a review issue after BLA submission. However, you would also need to address the safety requirements for a BLA submission discussed in the response to Question 4. Additionally, a future marketing application should include an efficacy analysis in the subset of AChR-antibody seronegative patients.	Study ARGX-113-1704 and the OLE Study ARGX-113-1705 enrolled a subset of AChR-antibody seronegative patients, per FDA's EoP2 advice. (b) (4) [redacted] **Argenx acknowledges FDA's response. No additional discussion required.**
2	Does the Agency agree to change the test statistics that was planned per protocol to compare efgartigimod and placebo with respect to time to qualification for retreatment?	We do not agree to change the test statistics post hoc based on observed data. The planned log-rank test is a valid test without proportional hazards assumption.	**Argenx acknowledges FDA's response. No additional discussion required.**
3	Does the Agency agree with the sponsor's proposed approach for the	It is unclear to us if the pooled efficacy analysis will provide useful information given the varied designs of the studies. You may include	**Argenx acknowledges FDA's response. No additional discussion required.**

	Sponsor Original Question	FDA Response	Argenx position/clarification
	presentation of efficacy data in the Summary of Clinical Efficacy (SCE)? The Integrated Summary of Efficacy (ISE) is planned to be included in the SCE.	a pooled analysis of efficacy in the submission in addition to the individual study results; however, our efficacy review would focus on the data from the Phase 3 study.	
4	Does the Agency agree with the proposed safety database included at the time of the planned BLA?	We do not agree. Your proposed safety database will not be adequate to support the submission of a BLA. In Table 5 of the briefing document, you report only 15 subjects with at least 12 months of follow-up for safety. Considering the prevalance of myasthenia gravis, your submission should be consistent with ICH E1 requirements that specify that 100 subjects be exposed to the drug for a minimum of one-year as part of a safety database. Additionally, as discussed at the End of Phase 2 meeting on April 17, 2018, it is required that "at least half of the safety consist of patients dosed with the highest anticipated dose and frequency of dosing." Based on your response to the information request submitted on July 21, 2020, more than half (50/96) of the patients exposed to efgartigimod have required 4 or more cycles of treatment during at least 6 months of follow-up (i.e., a treatment cycle of approximately every 6 weeks). Therefore, we anticipate that you will need, at a minimum, 12 months of safety data from approximately 50 subjects treated with a frequency of at least one cycle every 6 weeks (i.e., 8 cycles in 12 months), in addition to 12 months of safety data from 50 subjects at any treatment cycle frequency. A separate safety	Please refer to the clarification provided separately via email 31 July 2020.

	Sponsor Original Question	FDA Response	Argenx position/clarification
		study or a modification to the ongoing open-label study to include regularly scheduled dosing (e.g., every 6 weeks) could provide the necessary safety data.	
5	Does the Agency agree with the proposed content for the safety update and the timing of safety update submission?	You propose submitting the safety update as a 90-day safety update rather than a 120-day safety update, and to include TEAEs, clinical laboratory data, vital signs, ECGs, immunogenicity data, safety narratives, and pooled safety data from the Phase 2 and 3 studies. This plan may be acceptable, and can be considered once you have adequate safety data, as discussed in the response to Question 4.	**See clarification to Q4. Argenx will have safety data available at the time of the safety update report consistent with ICH E1.**
6	Does Agency agree with the sponsor's proposal regarding safety narratives and individual case report forms and with the proposed approach to the presentation of adverse events of special interest (AESI) in the planned BLA?	Your plan to provide safety narratives, CRFs, and AESIs is reasonable. Also, see response to Question 4. Also, please refer to the standard pre-BLA safety requests in Attachment 1. We note that not all requests may be applicable to your program; however, you should attempt to address the requests that are applicable.	**Argenx acknowledges FDA's response. No additional discussion required.**
7	Does the Agency agree that a risk Evaluation and Mitigation Strategy (REMS) or Medication Guide will not be required for efgartigimod, if approved for the proposed indication, and that the risks associated with treatment with efgartigimod can be managed adequately with appropriate labeling and routine pharmacovigilance activities?	At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.	**Argenx acknowledges FDA's response. No additional discussion required.**
8	Does the Agency agree with the sponsor's proposed approach for the	With respect to the safety pools, we note that the proposed pools may each contribute to the	**Argenx acknowledges FDA's response. No additional discussion required.**

	Sponsor Original Question	FDA Response	Argenx position/clarification
	presentation of safety data in the Summary of Clinical Safety (SCS)? The Integrated Summary of Safety (ISS) is planned to be included in the SCS.	understanding of safety. Please base your primary analysis on the pivotal phase 3 study with the safety pools included as supportive information. Also, see response to Question 4.	
9	Does the Agency agree with the proposed Study Data Standardization Plan (SDSP) for the nonclinical and clinical studies?	From a technical standpoint, the proposed Study Data Standardization Plan (SDSP) for the nonclinical and clinical studies is acceptable.	**Argenx acknowledges FDA's response. No additional discussion required.**
10	Does the Agency agree with the content and presentation of the BLA in support of efgartigimod for the treatment of patients with generalized myasthenia gravis (gMG)?	In general, the planned content and presentation of the BLA appear adequate, once you have adequate safety data, as discussed in the response to Question 4. Your justification for not conducting studies to assess the carcinogenic potential of efgartigimod is still under review. A response will be provided by July 31, 2020.	**Argenx acknowledges FDA's response. No additional discussion required. Thank you for providing your assessment on the carcinogenicity waiver.**
11	Does the Agency agree with the sponsor's proposal and schedule for submission of the CTD modules on a rolling basis?	Although rolling submission is allowed as part of Fast Track designation, it is premature to discuss specific submission dates, given the concerns with the safety database discussed in the response to Question 4.	**Argenx acknowledges FDA's response. Depending on our agreement to Question 4, this topic may be further discussed during the meeting.**
12	Does the Agency agree with the proposal for submission of BIMO listings?	You have proposed to include clinical study level information and subject-level data line listings by clinical site for studies ARGX-113-1704 and ARGX-113-1705, but not the summary-level clinical site dataset (clinsite). While submission of the clinsite dataset is currently optional, this dataset is useful in the Agency's decision-making for clinical site inspections. Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring	**Argenx acknowledges FDA's response. No additional discussion required.**

	Sponsor Original Question	FDA Response	Argenx position/clarification
		(BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications: https://www fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf https://www fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf	
13	The sponsor plans to request Priority Review for the planned BLA for efgartigimod in myasthenia gravis. Does the Agency agree that this BLA submission is eligible for Priority Review?	A request for priority review of your application will be considered at the time of filing, taking into account the information available at that time. We also remind you that there is available therapy for gMG; therefore, a request for priority review should describe how your product addresses an unmet need compared to available therapy.	**Argenx acknowledges FDA's response. No additional discussion required.**
14	The sponsor believes an Advisory Committee will not be required for efgartigimod in support of the myasthenia gravis indication. Does the Agency agree?	A determination regarding the need for an Advisory Committee meeting will be determined during review of your complete marketing application.	**Argenx acknowledges FDA's response. No additional discussion required, however, any insights and FDA's current thinking would be appreciated to help argenx plan for an AdComm, should one be needed.**
15	Is the Agency planning to schedule an application orientation meeting with the sponsor?	It is not common for the Division of Neurology 1 to request an application orientation meeting. The need for that meeting will be considered after your application has been submitted.	**Argenx acknowledges FDA's response. No additional discussion required.**
	Additional Information: Non-proprietary name guidance	To the extent that your proposed 351(a) BLA is within the scope of this guidance, FDA will assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.	**Argenx submitted a request for review of the four-letter suffix on 10 July 2020 . Can the Agency clarify when argenx might receive confirmation whether the proposed suffix was accepted? In addition, can the Agency provide guidance when a BLA license number might be provided in relation to BLA review. This would help argenx in subsequent planning once the BLA is submitted for review.**

Attachment 3.

18 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ERIC P BASTINGS
08/26/2020 12:50:23 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 132953

MEETING MINUTES

Argenx BVBA
c/o Cardinal Health Regulatory Sciences
Attention: Kaitlyn Riffel, MSc, RAC
Scientist III, Global Regulatory Affairs
7400 W 110th Street, Suite 300
Overland Park, KS 66210

Dear Ms. Riffel:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ARGX-113.

We also refer to the meeting between representatives of your firm and the FDA on April 17, 2018. The purpose of the meeting was to discuss the nonclinical and clinical aspects of the development for ARGX-113 for the treatment of patients with generalized myasthenia gravis.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact Fannie Choy, Regulatory Project Manager, at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Eric Bastings, M.D.
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End of Phase 2
Meeting Date and Time:	April 17, 2018, 10:00 a.m. – 11:00 a.m. EDT
Meeting Location:	White Oak Building 22, Conference Room: 1309
Application Number:	IND 132953
Product Name:	ARGX-113
Indication:	Generalized myasthenia gravis
Sponsor/Applicant Name:	Argenx BVBA
Meeting Chair:	Billy Dunn, M.D.
Meeting Recorder:	Fannie Choy, R.Ph.

FDA ATTENDEES

Division of Neurology Products
Billy Dunn, MD, Director
Eric Bastings, MD, Deputy Director
Teresa Buracchio, MD, Clinical Team Leader
Rainer Paine, MD, PhD, Clinical Reviewer
Fannie Choy, RPh, Regulatory Project Manager

Office of Biotechnology Products
Jee Chung, PhD, Quality Reviewer

Office of Clinical Pharmacology
Sreedharan Sabarinath, PhD, Clinical Pharmacology Team Leader
Bilal AbuAsal, PhD, Clinical Pharmacology Reviewer

Office of Biostatistics
Kun Jin, PhD, Team Leader, Division of Biometrics I
Xiang Ling, PhD, Statistical Reviewer, DBI

Office of Orphan Products Development
CAPT Jeff Fritsch, RPh, Regulatory Review Officer

Office of Surveillance and Epidemiology (OSE)
Monique Killen, Safety Regulatory Project Manager

SPONSOR ATTENDEES

Argenx BVBA
Keith Woods, Chief Operation Officer
Nicolas Leupin, MD, MBA, Chief Medical Officer
Antonio Guglietta, MD, Senior Medical Director
Peter Ulrichts, PhD, Research Follow
Torsten Dreier, PhD, Chief Development Officer
Monika Van Den Haute, MSc, Senior Regulatory Affairs Manager
(b) (4) Regulatory Affairs, Consultant
Katrien Verschueren, MSc, Senior Biostatistician
(b) (4) Biostatistician Expert, Consultant

(b) (4)

1.0 BACKGROUND

Argenx BVBA (Argenx) is developing ARGX-113, a human anti-neonatal Fc receptor (FcRn) IgG1 Fc fragment, for the treatment of myasthenia gravis (MG).

(b) (4) Argenx submitted the initial IND application under the current IND 132953 on March 17, 2017, and the proposed clinical investigation was determined safe to proceed on April 14, 2017.

Argenx has completed a Phase 1 study (ARGX-113-1501) in healthy volunteers and a Phase 2 study (ARGX-113-1602) in MG patients. The sponsor has requested this EOP2 meeting to obtain the Division's feedback on its nonclinical and clinical development plan, including clinical pharmacology plan. A separate CMC EOP2 meeting is scheduled in May 2018.

The Agency granted Orphan Drug designation for ARGX-113 for the treatment of MG in September 2017.

FDA sent Preliminary Comments to Argenx on April 12, 2018.

2. DISCUSSION

2.1. Nonclinical

Question 1:

Does the Agency concur that the proposed non-clinical program, which includes the completed single- and repeat-dose toxicity studies, and planned reproductive and developmental toxicity studies, is adequate to support the proposed Phase 3 study and future registration of ARGX-113 for the treatment of gMG?

FDA Response to Question 1:

Based on the information provided in your briefing package, we have the following comments:

1) We note your plan to not conduct carcinogenicity studies of ARGX-113. However, you should submit a request for waiver of the requirement to assess the carcinogenic potential of ARGX-113, with a detailed justification and all supportive data.
2) The adequacy of the completed nonclinical studies to support clinical studies of ARGX-113 manufactured from the new cell line will depend on your ability to document comparability between material from the current and new cell lines.

Meeting Discussion: There was no meeting discussion.

2.2. Clinical Pharmacology

Question 2:

Does the Agency agree with the Sponsor's proposed testing strategy for measuring binding and neutralizing anti-drug antibodies as integral part of the immunogenicity risk assessment?

FDA Response to Question 2:

The three-tiered (screening, confirmatory, and titration) testing strategy described in the meeting package for patient samples for anti-drug antibodies (ADA) appears acceptable. However, regarding the neutralizing activity testing strategy, based on the last sentence on page 68 of the meeting package, "In cases where titers are significantly increasing over time, ADA will be characterized in a neutralizing assay...", it is unclear if all confirmed positive ADA samples will be characterized for neutralizing activity or for only the samples that showed increasing titers over time. If it is the latter case, then FDA recommends that all confirmed positive ADA samples be analyzed for neutralizing activity in order to understand and correlate the impact of the ADAs on product safety and efficacy.

Meeting Discussion: There was no meeting discussion.

Question 3:

Does the Agency concur that the clinical pharmacology plan is adequate to support registration?

FDA Response to Question 3:

The clinical pharmacology plan seems acceptable; however, you should include a plan to evaluate potential drug interaction between ARGX-113 and other therapeutic monoclonal antibodies. Based on the information you presented, the impact of impairment in organ function on the exposure to ARGX-113 is considered low. Therefore, you can include subjects with renal/hepatic function impairment in the proposed Phase 3 study.

Meeting Discussion:

The sponsor commented [redacted] (b) (4) The Agency clarified that this approach is not adequate and the label should provide clear recommendations on dose adjustments or spacing of dose administration to minimize interactions with other monoclonal antibodies. The sponsor suggested submitting PK/PD data to evaluate the effect of ARGX-113 exposure on total IGg levels. The Agency recommended that the sponsor submit their written proposal to assess and manage the drug-drug interaction liability of ARGX-113 for review.

2.3. Clinical Efficacy and Safety

Question 4:

Does the Agency concur with the design of the proposed pivotal Phase 3 Study ARGX-113-1704, including:

a. The patient population?

b. The inclusion and exclusion criteria?

c. The primary endpoint?

d. The secondary endpoints?

e. The dose and dose regimen for the proposed Phase 3 study?

f. The statistical methodology?

FDA Response to Question 4:

Given the chronic nature of myasthenia gravis and the pharmacokinetic profile of ARGX-113, your proposed dosing (b) (4) does not appear to be justified. We recommend that you conduct a placebo-controlled trial of at least 3 months' duration with regularly scheduled dosing (e.g., weekly). Although the Myasthenia Gravis Activities of Daily Living scale (MG-ADL) is a suitable measure of efficacy, we recommend that the primary efficacy endpoint be the mean change from baseline between treatment groups in the MG-ADL total score instead of a responder definition based on a pre-specified score change. The study design should also standardize the concomitant therapies given during the study and stratify randomization based on them.

4a. The proposed patient population appears to be acceptable.

4b. We have the following comments regarding your inclusion and exclusion criteria:

- A clear definition of "inadequate response to current therapy" should be added to the inclusion criteria.
- The current inclusion criteria state that "Patients should have an MG-ADL score of ≥ 5 points with more than 50% points due to non-ocular symptoms at Screening and Baseline." Please clarify your rationale for choosing a 5-point threshold.
- Rituximab and eculizumab should be named in the exclusion criteria under "Use of any monoclonal antibody for immunomodulation within 6 months prior to first dosing." Also, this exclusion of monoclonal antibody use should be a universal exclusion criterion, and not left to the "opinion of the Investigator" that it would interfere with data interpretation.
- Inclusion criterion #6 for AZA in the submitted protocol states "treatment initiated at least x months ago and no dose changes in the last x months before Screening." You need to define "x" for AZA and also for "Other NSIDs" and "Steroids" (p. 154 of meeting background materials).

4c. Please see comment above. The scoring of the MG-ADL should be performed by a trained and certified clinical evaluator.

4d. The secondary endpoints appear acceptable, on face. Although the Quantitative Myasthenia Gravis (QMG) scale is a suitable secondary endpoint, we recommend that the endpoint be assessed as the mean change from baseline in the QMG total score instead of a responder definition based on a pre-specified score change.

4e. Please see comment above. We also encourage you to explore a wider range of doses in your proposed study to allow for appropriate dose-response relationships to be evaluated.

4f. It is premature to comment on statistical methodology until an agreement has been reached on the study design.

Meeting Discussion:

The meeting opened with a presentation (b) (4) who provided an overview of the treatment approaches for myasthenia gravis. He noted the need for flexibility in dosing regimens based on changing patient symptoms and clinical exam findings. For example, although IVIg and plasmapheresis are often used intermittently for acute exacerbations of myasthenia gravis, they may also be administered chronically in some patients.

The sponsor stated that they intend to develop ARGX-113 for intermittent dosing and they indicated that they would seek labeling to allow for "as needed dosing". The Agency stated that a 3-month study with the proposed regimen (4 weekly doses) may be acceptable to demonstrate efficacy; however, there will likely be variability of duration of the drug's effect and the optimal dosing regimen is not yet known. Some patients may need chronic regular administration of ARGX-113. If it is found during the extension study that some patients require regular administration of ARGX-113, additional safety data may be required to support the more frequent dosing. Typically, it would be required that at least half of the safety database consist of patients dosed with the highest anticipated dose and frequency of dosing. A separate safety study with scheduled dosing (e.g., every 2 to 3 months) could be considered to enrich the safety database. The Agency referred the sponsor to the development program of intermittent botulinum toxin injections as an example of a safety database for a chronic intermittent dosing regimen.

The sponsor stated that enrollment in the open-label extension (OLE) study will be optional for patients enrolled in the pivotal study. The Agency recommended that the extension study be integrated into the pivotal study under a single protocol that requires participation in the extension study because it is critical to the drug development program. Blinding should be maintained during the extension study. The Agency recommended against changing concomitant treatment dosing during the extension study because it could confound the results. The Agency reiterated its recommendation to standardize the concomitant therapies given during the study and stratify randomization based on them, as imbalances in background medications would affect the interpretability of the study results. The number of allowed background medications should also be kept to a minimum.

The Agency noted that IVIg is given intermittently based on a patient's response, in a manner analogous to the proposed dosing of ARGX-113; however, the proposed study population has a milder disease severity than patients who are typically treated with IVIg. The sponsor responded that they thought that the safety profile would likely allow for use in a milder patient population than those treated with IVIg.

The sponsor inquired about the Agency's rationale for recommending the use of the mean change from baseline between treatment groups in the MG-ADL total score for the primary endpoint instead of a responder definition. The sponsor prefers to use a responder definition because of the planned intermittent and variable dosing frequencies that will be assessed in the

pivotal and extension studies. The Agency responded that the mean change is more sensitive to change and that data can be lost with a responder definition; however, the Agency agreed that the proposed responder definition for the MG-ADL would also be acceptable for the efficacy trial.

The sponsor stated that it plans to include 15% antibody-negative myasthenia gravis patients in the pivotal study. The Agency recommended that the sponsor power the study for the antibody-positive population but increase the number of antibody-negative patients enrolled to 20%.

The sponsor may submit a study synopsis and draft statistical analysis plan to the IND for Agency feedback outside of a formal meeting request.

Question 5:

Does the Agency agree with the objective and design of the Phase 3 follow-up Study ARGX-113-1705?

FDA Response to Question 5:

See the response to Question 4. Study ARGX-113-1705 would be inadequate to assess chronic safety or efficacy. The long-term extension study should assess the same dosing regimen that is used in your Phase 3 trials.

Meeting Discussion: See the discussion for Question 4.

Question 6:

Does the Agency concur that the projected overall safety database is adequate for registration?

FDA Response to Question 6:

See the responses to Questions 4 and 5. Your proposed safety database must be based on the dosing regimen that is used in your Phase 3 trials. In general, a safety database should be consistent with ICH E1 requirements to support a marketing application; however, there may be some flexibility in these requirements for rare diseases, such as myasthenia gravis. The adequacy of your safety database should be discussed at a future meeting once the results of your pivotal trials are available.

Meeting Discussion: There was no meeting discussion.

Question 7:

Does the Agency agree that the proposed clinical development program supports registration of ARGX-113 (b) (4)

FDA Response to Question 7:

See responses to Questions 4 and 6.

(b) (4)

You propose registration with only a single adequate and well-controlled investigation. A single trial can be the basis for marketing approval under specific circumstances discussed in the Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, available at:

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072008.pdf.

The acceptability of a single trial to support drug approval depends on the study results, and cannot be determined prospectively.

Meeting Discussion: There was no meeting discussion.

Question 8:

(b) (4)

FDA Response to Question 8:

(b) (4)

a discussion of specific labeling language is premature and will be a matter of review following BLA submission.

Meeting Discussion: There was no meeting discussion.

Question 9:

Does the Agency agree that, if statistical significance is achieved, data from the secondary endpoints from Phase 3 Study ARGX-1704 will be reflected in the Clinical Studies Section of the Prescribing Information?

FDA Response to Question 9:

A discussion of labeling language is premature and will be a matter of review at the time of a BLA submission. In general, for secondary endpoints to be considered appropriate for inclusion in any future product label, they should assess domains that are distinct from those evaluated by the primary endpoint. In addition, the analysis of the endpoints must be statistically controlled for Type I error.

Meeting Discussion: There was no meeting discussion.

Question 10:

Does the Agency agree that, if clinically meaningful data regarding duration of treatment effect are obtained from Phase 3 Studies ARGX-113-1704 and ARGX-113-1705, that these data may be described in the Clinical Studies Section of the Prescribing Information?

FDA Response to Question 10:

See the responses to Questions 4 and 5.

Meeting Discussion: There was no meeting discussion.

2.4. Question Regarding Orphan Drug Exclusivity

Question 11:

Does the Agency agree with the Sponsor's conclusion that under the Orphan Drug Regulations, should an orphan drug-designated conventional monoclonal antibody targeting FcRn be approved for the same indication, such an approval would not be exclusive as pertains to ARGX-113?

FDA Response to Question 11:

The Agency concurs with the sponsor's interpretation. Please keep in mind that a final determination for exclusivity/sameness will be made at the time of marketing approval for ARGX-113. OOPD will work closely with DNP on the final determination for orphan-drug exclusivity at the time marketing approval is granted for ARGX-113.

Meeting Discussion: There was no meeting discussion.

3.0 ADDITIONAL COMMENTS

PROSPECTIVE ASSESSMENTS OF SUICIDAL IDEATION AND BEHAVIOR IN CLINICAL PROTOCOLS

Treatment-emergent suicidal ideation and behavior have been identified as a concern for a number of drugs and drug classes. For example, meta-analyses of clinical trial data for both antiepileptic drugs and antidepressants have demonstrated that these drugs increase the risk of suicidal ideation and behavior. Spontaneous reports have led to similar concerns with other drugs as well, e.g., isotretinoin and other tretinoins, beta blockers, reserpine, smoking cessation drugs, and drugs for weight loss. Because of these concerns, a prospective assessment for suicidal ideation and behavior should be included, when appropriate and feasible, in clinical trials involving all drugs and biological products for neurological indications. These assessments should generally be included in every clinical protocol, at every visit, and in every phase of development, with the exception of single-dose trials in healthy volunteers. These assessments should be conducted whether or not a particular product is known or suspected to be associated with treatment-emergent suicidal ideation and behavior. A sponsor considering the omission of the assessment of suicidal ideation and behavior from a particular clinical protocol should prospectively discuss this omission with the Division of Neurology Products.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards

specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of **May 5, 2017,** the following submission types: **NDA, ANDA,** and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the Guidance for Industry, *Assessment of Abuse Potential of Drugs*, available at:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

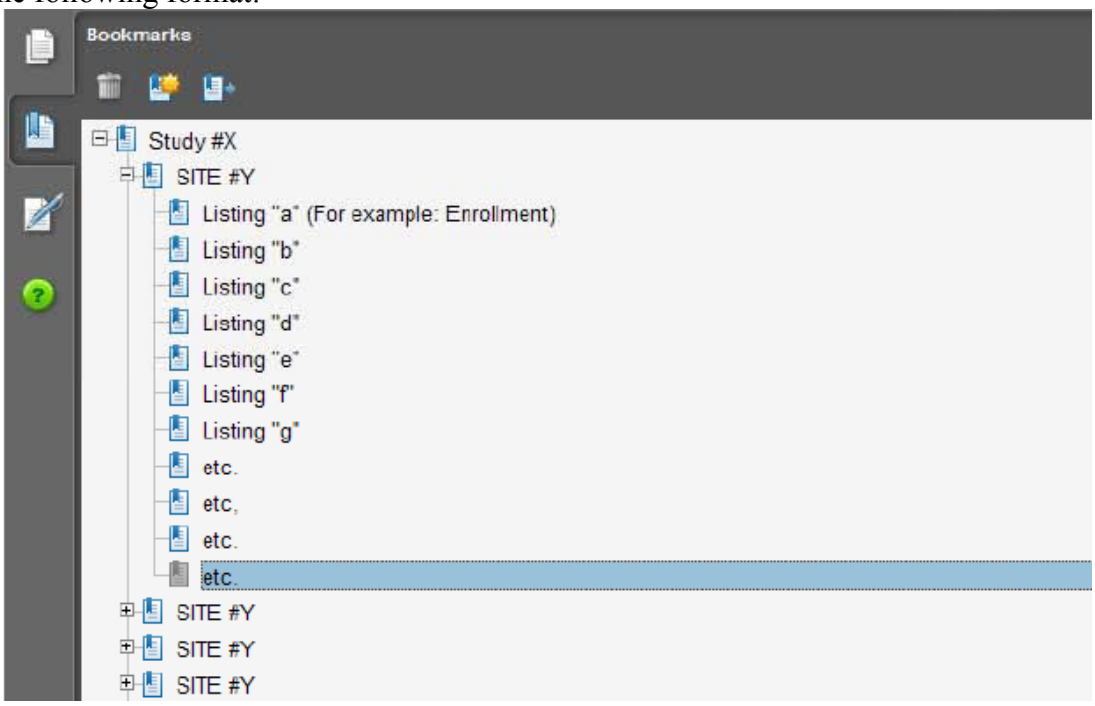
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)

j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed

and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERIC P BASTINGS
04/26/2018